

The University of Chicago

THE RELATIVE REACTIVITIES OF
ALDEHYDES AND KETONES

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE PHYSICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1937

By

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The author wishes to acknowledge his great indebtedness to Professor M. S. Kharasch for guidance and invaluable advice in connection with this study. He also desires to express his sincere thanks to Dr. F. R. Mayo for his constant interest and suggestions.

INTRODUCTION

A comparison of the reactivities of aldehydes and ketones has been the subject of numerous investigations.¹ The results of these studies, however, are of limited usefulness, mostly because the early investigators did not recognize that relative reaction velocities and reactivities are not always in mutual agreement. Because of this limitation and for reasons which will be apparent in the following discussion, the early work in this field will not be reviewed in great detail.

It was early recognized by Menshutkin that the initial velocity of a reaction and the total amount of substance formed after the reaction has run its course do not stand in any simple relation to one another. Yet Petrenko-Kritschenko based his conclusions merely on the yields of reaction product obtained after the lapse of a definite time interval. Stewart, who used a somewhat similar method, recognized its shortcomings, particularly when applied to reversible reactions such as the formation of bisulfite compounds.² Nevertheless, it is of interest to compare some of the results obtained by these investigators. In Table I the ketones are arranged in order of decreasing activity toward semicarbazide salts, as found by Michael.³

It is apparent from the table that there are great differences in the relative reaction rates found by the various methods. Although the relative rates found by the methods of Stewart and Petrenko-Kritschenko agree fairly well (with minor exceptions), they differ markedly from the series developed by Michael. The reason for these discrepancies may be more clearly understood from a consideration of the following factors, which influence the results in condensation reactions under consideration:

¹The most important references may be found in:

Michael, J. Am. Chem. Soc., **41**, 393-424 (1919).

Conant and Bartlett, ibid., **54**, 2881 (1932).

²Stewart, Stereochemistry (London: Longmans, 1908), 478.

³Michael, op. cit., p. 404.

TABLE I
REACTIVITIES OF KETONES

Ketone	Velocities ^a				
	NH ₂ OH ^b	NaHSO ₃ ^c	C ₆ H ₅ NHNH ₂ ^d	NH ₂ OH ^c	KHSO ₃ ^e
CH ₃ COC ₆ H ₁₁			31	67.6	5.7
CH ₃ COC(CH ₃) ₃	24.5	5.6	3.6		
CH ₃ COC ₃ H ₇	39.9	23.4	38	74.6	12.4
CH ₃ COC ₂ H ₅	39.2	36.4	52	79.2	14
CH ₃ COCH ₃	50.0	56.2	66	82	22
C ₂ H ₅ COC ₂ H ₅			11	37.9	1.8
C ₃ H ₇ COC ₃ H ₇			7.5	31.4	0.0
C ₂ H ₅ COC ₃ H ₇			10	36.8	2.0
CH ₃ COCH(CH ₃) ₂	32	12.3	15	33	2.7
C ₂ H ₅ COCH(CH ₃) ₂			3.7	28.9	

^aPer cent converted in definite period of time.

^bThirty-minute velocities.⁴

^cSixty-minute velocities.⁵

^dAmount formed in one hour in 50% alcohol with a 0.01 N solution.⁶

^eSame as in previous statement.⁷

- a) The solubility of the final reaction product. In the work of Petrenko-Kritschenko and the early work of Stewart conclusions are based on the yield of the "insoluble" addition product.
- b) The equilibrium of the reaction. All the reactions thus far discussed reach a state of equilibrium. The equilibrium proper, as well as the time required for the attainment of this state, varies with the nature of the reacting substances. The investigations of both Stewart and Petrenko-Kritschenko ignore this factor. Michael also does not give it adequate consideration.

⁴Stewart, J. Chem. Soc., **87**, 410 (1905).

⁵Stewart, ibid., p. 185.

⁶Petrenko-Kritschenko, et al., Ann., **341**, 150 (1905).

⁷Petrenko-Kritschenko, et al., J. Russ. Phys. Chem. Soc., **36**, 1505 (1904).

- c) The hydrolysis of the condensation product. The products of all of the aforementioned reactions are hydrolyzable to various degrees depending to a large extent on the acidity of the medium. This factor has been ignored in the above investigations.
- d) The acidity of the medium affects the rate of the reaction, the equilibrium, and the hydrolysis of the final product. In the early work no attempt was made to control the hydrogen-ion concentration. Later investigators used buffers to counteract pH changes.

Since Michael's results were not based on the yields of the reaction products, the objection raised by a consideration of the solubility factor does not apply. His definition of reactivity is, however, unique. Thus, he considers the most reactive carbonyl compound to be that which reacts with the semicarbazide salt of the strongest acid in the most acidic medium. For example, a ketone reacting with semicarbazide hydrochloride in 0.5 N hydrochloric acid is considered more reactive than one which does not react under these conditions, although the latter may react with the same semicarbazide salt to which no acid has been added. Similarly, a ketone reacting with semicarbazide hydrochloride is more reactive than one which reacts only with the oxalate (a salt of a weaker acid). This classification is based on somewhat arbitrary considerations, and is very limited in its application.

Conant and Bartlett⁸ have shown that the following conditions must be met in order to compare the reaction rates and equilibria of a series of aldehydes and ketones with the same nitrogen base:

- a) The nitrogen base and the condensation product must be present in the form of the free base.
- b) The concentration of the catalyst must be carefully controlled. These investigators have measured the velocity constants of formation and hydrolysis, as well as the equilibrium constant for the hydrolysis, of a series of semicarbazones. The relative reactivities of the aldehydes and ketones may then be deduced from a consideration of the velocity constants of formation.

This investigation has been extended by Westheimer,⁹ who

⁸Conant and Bartlett, *op. cit.*, pp. 2882-94.

⁹Westheimer, *J. Am. Chem. Soc.*, **56**, 1962-5 (1934).

carried out similar determinations with 60% methyl cellosolve as the solvent. His results are given in the following table. The compounds are arranged in the order of decreasing activity found in my investigation:

TABLE II
RATES OF FORMATION OF SEMICARBAZONES

Carbonyl Compound	Velocity Constant of Formation		
	Acetate ⁹ Buffer	Chloracetate ⁹ Buffer	Water ¹⁰ pH 7
Acetone	5.92	23.2	6.02
Acetaldehyde			361
Benzaldehyde	5.1	145	2.05
Pinacolone	0.41	1.48	0.068
Cyclohexanone	24.9	fast	36

A consideration of the above results reveals that both the hydrogen-ion concentration and the nature of the solvent are important factors in the determination of the relative reactivities. Although the direction of change of reactivity with change of medium is the same for similar compounds, yet the magnitude of the change may differ greatly. Consider, for example, the case of acetone and benzaldehyde. In water (pH 7) the ketone is about three times as reactive as the aldehyde (in excellent, but perhaps fortuitous, agreement with the results of the current investigation¹¹). In the acetate buffer the reactivities are more nearly alike, though slightly greater for acetone. In the more acidic chloracetate buffer the reactivities of both are increased. In the case of benzaldehyde the increase in reaction velocity is about thirty-fold, while that for acetone is only about five-fold. The net result of this change is that benzaldehyde is about six times as reactive as acetone in the chloracetate buffer. These results indicate that the relative reactivities of a series of compounds toward a given reagent in a particular solvent may be radically altered in another medium, and extreme caution should be exercised in using reactivity data for predictive purposes.

⁹Ibid.

¹⁰Conant and Bartlett, op. cit., p. 2896.

¹¹Infra, Table IX.

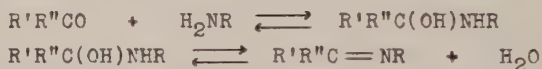
The only recorded investigation of relative reactivities of carbonyl compounds on the basis of competitive reactions is that of Hibbert.¹² In that work the ketone was mixed with α -naphthol, the mixture dissolved in phenetole and allowed to react with a solution of methylmagnesium iodide in phenetole. The relative reactivities of the ketones were determined from the volume of methane evolved in each case. Since the methane evolved is a measure of the extent of reaction of the α -naphthol with the Grignard reagent, the difference in volume from that evolved with the equivalent amount of α -naphthol alone constitutes a measure of the extent of reaction of the ketone with the reagent. The greater this difference (i.e., the less the total volume of methane evolved), the greater is the reactivity of the ketone. The series obtained in this manner agrees rather satisfactorily with those of Stewart and Petrenko-Kritschenko, but shows marked deviations from that obtained by Michael.

¹²Hibbert, J. Chem. Soc., 101, 341-4 (1912).

DISCUSSION

In the foregoing review the effort was made to show the rather unsatisfactory status of the information available on the reactivities of aldehydes and ketones. These data must of necessity be of limited applicability, because of the complex nature of the reactions used (particularly in the case of condensations with nitrogen bases) and because the reactions studied are catalyzed by acids. The preferred mode of approach to this problem is undoubtedly by competitive reactions; i.e., by allowing two carbonyl compounds to compete for the same reagent and determining the relative yields of the two products. Furthermore, if a reactivity series is to have any appreciable range of application at all, it should be based on a reaction which is not dependent upon a catalyst. Accordingly, the study of the relative reactivities of aldehydes and ketones, based on competitive reactions with the Grignard reagent, was undertaken.

In the work with nitrogen bases the following reactions must be considered:



Conant and Bartlett⁸ found that the first reaction is comparatively slow and therefore determines the rate, while the second reaction follows instantaneously. Nevertheless, in this type of work four important reactions must be considered, as the reverse reactions should not be ignored. If, instead of the free bases, the salts are used, the situation becomes even more complex.

In the condensation with the Grignard reagent, however, only one fundamental reaction need be considered; i.e., the condensation reaction proper and the effect of catalysts thereon:



Under appropriate conditions (solvent, temperature, and concentration) the rate of this reaction is determined by the nature of the carbonyl compound and the Grignard reagent. If the Grignard reagent be the same for a series of such reactions, and only the nature of the carbonyl compound altered, then the differences in

rate of condensation could be attributed to the differences in reactivity of the carbonyl compounds.

Although the Grignard reagent, in ether solution, is actually in the form of an oxonium salt, still its behavior is identical with that of the free organomagnesium halide.¹³ Furthermore, the equilibrium which exists in an ether solution of a Grignard reagent:¹⁴ $2 \text{RMgX} \rightleftharpoons \text{R}_2\text{Mg} + \text{MgX}_2$, has very little bearing on the final results of my study. This has been shown by the consistent results of experiments in which the concentrations of the Grignard reagent were altered considerably.¹⁵ In the same solvent and at constant temperature, any changes in this equilibrium must then be attributed to the action of the carbonyl compound. The same is true of differences in stability of the oxonium salt of the Grignard reagent. In all cases the effect on the equilibrium will be such as to promote the condensation reaction with the more reactive carbonyl compound. Furthermore, since the hydrolysis of the condensation product with a suitable reagent (an instantaneous reaction) destroys any unreacted Grignard reagent and thereby terminates the condensation process, the rate of the reaction is determined by the rate of condensation of the Grignard reagent with the carbonyl compound.

Comparative reactivities of aldehydes and ketones toward the Grignard reagent.--The Grignard reagent selected for this study was phenylmagnesium bromide, since it does not reduce ketones and because the rate of addition to carbonyl compounds is sufficiently slow to permit the ready detection of differences in reactivity.¹⁶ If the Grignard reagent were one that adds rapidly, then the observed difference in reactivity of the competing carbonyl compounds would be expected to be less marked. This was verified by comparing the relative reactivities of cyclohexanone and benzaldehyde with both phenylmagnesium bromide and benzylmagnesium chloride.¹⁷ Both Grignard reagents are non-reducing, but

¹³Waters and Lowry, Physical Aspects of Organic Chemistry (New York: Van Nostrand, 1936), 165.

¹⁴Schlenk and Schlenk, Ber., **62**, 920-4 (1929).

Gilman and Fothergill, J. Am. Chem. Soc., **51**, 3149 (1929).

¹⁵Infra, Tables VIII and XII.

¹⁶Kharasch and Weinhouse, J. Org. Chem., **1**, 209-30 (1936).

¹⁷Infra, Tables VIII and XII.

the rate of addition is much more rapid in the case of the latter. Whereas benzaldehyde was found to be more than five times as reactive as cyclohexanone toward phenylmagnesium bromide, yet it was apparently only one and one-half times as reactive as cyclohexanone toward benzylmagnesium chloride.

Experimental method of this work.--The procedure adopted in this study was to add the Grignard reagent to the solution of the two competing carbonyl compounds, the mole ratio of Grignard reagent to each of these being 10:7:7. At first glance it might be expected that the maximum reactivity ratio obtainable for any pair of compounds would be 7:3. For, if compound A reacts completely with the Grignard reagent (during which time the reaction of compound B is slow), then if the reagent is completely used up by the carbonyl compounds at the time of hydrolysis, this ratio would prevail. In practice this is not so. Although the addition reaction is very rapid at the beginning, the rate decreases after a portion of the reagent has been added. In fact the addition reaction proper may not be complete even four hours after the last of the Grignard reagent solution has been introduced into the mixture. As an illustration may be cited the total yields obtained in the reactions of benzaldehyde and cyclohexanone. When these compounds react with phenylmagnesium bromide, the total yield after four hours is 50%, but with benzylmagnesium chloride the yield is over 80% in the same period. These results are in accord with the more rapid rate of addition of benzylmagnesium chloride.

The Grignard reagent was prepared in the usual manner, and the solution filtered after cooling to room temperature. The total amount of Grignard reagent available for addition was determined by the acid titration method,¹⁸ using 2 cc. aliquots of this solution. The solution of the carbonyl compounds was then prepared, such that the mole ratio of Grignard reagent to each of these was 10:7:7. The solution of the Grignard reagent was introduced slowly, with constant agitation and cooling of the mixture. After standing the requisite period of time, the mixture was hydrolyzed with the appropriate reagent, and the products were extracted with ether.

¹⁸Gilman, Zoellner and Dickey, J. Am. Chem. Soc., **51**, 1577 (1929).

Analysis of reaction mixture.--In the ether extract were isolated:

- a) The secondary alcohol formed by condensation of the aldehyde with the Grignard reagent.
- b) The tertiary alcohol formed by condensation of the ketone with the Grignard reagent.
- c) Unreacted aldehyde and ketone.

The secondary alcohol was determined by acetylation, and any unchanged aldehyde or ketone were determined by appropriate methods. Complete details will be found in the experimental part.

Test for completeness of reaction.--In my initial experiments it was desired to determine the extent of reaction by testing for the presence of unreacted Grignard reagent in the mixture. Use was made of the color test described by Gilman and Schulze;¹⁹ but unfortunately the test was found to be unreliable for this purpose. Within a few minutes after the introduction of the Grignard reagent into the reaction mixture, a portion of the supernatant liquid was tested for the presence of free Grignard reagent. The color test was invariably negative, apparently indicating the absence of unreacted Grignard reagent. Yet the presence of large quantities of the Grignard reagent could be demonstrated by treating the supernatant liquid with an ether solution of mercuric chloride and subsequently isolating the organomercury halide of the Grignard reagent. The limitations of the color test are discussed further in the Experimental Part.

Discussion of Results

The order of relative reactivities obtained in this study is given in Table III. The reactivity indices are purely arbitrary and are based on the average values obtained in the experiments. The value for cyclohexanone was taken as unity.

It is interesting to compare this order of reactivity with that obtained by Conant and Bartlett. Acetaldehyde, which these investigators found to be the most reactive in the series, is here second to acetone. The only other disagreement is the case of cyclohexanone. Conant and Bartlett placed it second to acetaldehyde, but it is here found to be the least reactive of all the compounds investigated.

¹⁹Gilman and Schulze, J. Am. Chem. Soc., **47**, 2002 (1925).

TABLE III
RELATIVE REACTIVITIES OF ALDEHYDES
AND KETONES

Compound	Reactivity ^a
Acetone.....	15.5
Acetaldehyde.....	10.8
Benzaldehyde.....	5.4
Pinacolone.....	4.8
Cyclohexanone.....	1.0

^aThe reactivity ratios for the various pairs of compounds used in the competitive reactions may be found in the Experimental Part.

The data presented are probably inadequate to warrant any generalized interpretation regarding these differences; but a consideration of the results obtained by Westheimer in the case of benzaldehyde and acetone may throw some light on the problem. In the same medium (60% methyl cellosolve) in the acetate buffer the acetone is slightly more reactive; but in the more acidic chloracetate buffer (approximately a change of three pH units), the order is reversed and the aldehyde is found to be about six times as reactive as the ketone. Obviously, the reaction is catalyzed by hydrogen-ion, since the velocities of reaction in both cases increase with increased hydrogen-ion concentration. If the effect of hydrogen-ion were solely on the carbonyl group, it would be expected that the magnitude of change would be approximately the same in each case. The fact that this is not true indicates that the effect on the addendum of the carbonyl compound is at least of equal importance. The magnitude of this effect may vary greatly with different carbonyl compounds. Hence the order of reactivity compiled from velocity data for a reaction catalyzed by hydrogen-ion is of limited applicability.

It is significant that even in the competitive Grignard reactions a reversal of order is obtainable with change of solvent. Whereas acetone was found to be almost three times as reactive as benzaldehyde in anhydrous ether, yet in pyridine the order was reversed and the benzaldehyde was found to be about one and one-third times as reactive.²⁰

²⁰Infra, Tables IX and XIII.

Many hypotheses suggest themselves to account for this difference observed in pyridine solution. These are based on:

- a) The enhanced enolization of the acetone in pyridine.
- b) The dissociation of the Grignard reagent.¹⁴
- c) The formation of molecular compounds of pyridine.²¹

However, upon the basis of the evidence thus far available it is impossible to decide in favor of any one hypothesis.

Conclusions.--These experiments serve to emphasize the necessity for clearly defining the conditions under which the reactivities of any series of compounds are to be considered. Unless the solvent, reaction, and the catalytic agent are specified, relative reactivity can be of little value and meaning.

²¹ Oddo, Gazz. chim. ital., **37** (2), 356 (1907).

Pfeiffer, Organische Molekülverbindungen (Stuttgart: Ferdinand Enke, 1927), 55.

EXPERIMENTAL PART

Preparation of reagents.--The anhydrous ether was prepared by washing the commercial product with a dilute water solution of potassium permanganate (saturated with sodium chloride) until no further discoloration resulted. The ether was dried for twenty-four hours over calcium chloride, and then decanted and dried over sodium wire. After the evolution of hydrogen had ceased, the ether was distilled from the sodium into a dark stock bottle, in which it was stored over sodium wire. All chemicals used in the experiments were carefully purified prior to use.

Technique of filtration of the Grignard reagent.--The Grignard reagent was prepared in the usual manner in a three-necked flask. Early attempts to filter the reagent by using the special type of flask described by Kharasch and Weinhouse²² met with little success, as the sintered glass disc (100 mesh) became quickly clogged with fine suspended matter. Application of slight pressure by dry nitrogen was of little assistance. The difficulty was overcome by the use of a specially constructed all-glass siphon, which was held in place by tightly fitting rubber stoppers in the reaction flask and the receiving vessel respectively. The end of the siphon dipping into the Grignard flask contained a small sintered glass plate (100 mesh, 8 mm. diameter). The receiving end consisted of a vacuum adapter, which permitted the application of suction to the system and which conducted the solution directly from the inner glass tube to the receiving vessel. The siphon proper was constructed of 6 mm. (outer diameter) tubing, which size was found to be most satisfactory for the purpose. This method of filtration has several advantages over that previously described:²²

1. The suspended particles settle to the bottom of the Grignard flask and do not tend to clog the sintered plate.
2. This method is much more convenient. No elaborate system for drying and purifying the gas is necessary. The rate of filtration is more readily controlled. The experimenter is not

²²Kharasch and Weinhouse, op. cit., p. 224.

required to contend with the blowing-out of stoppers, a frequent occurrence when the gas pressure is increased. The filtration proper is much more regular and certain.

3. The siphon is very easily cleaned by immersion in sodium dichromate--sulfuric acid mixture. If necessary, it may be boiled in this or other cleaning mixtures. Of course, the siphon must be broken at one point to remove the stoppers prior to cleaning. When the parts of the siphon are clean and dry, the stoppers are replaced and the two sections of the siphon sealed together. Obviously, the special type of flask described²² cannot be easily subjected to these operations, and it has been found that the portion of the flask between the sintered plate and the stopcock is not readily and quickly cleaned by mere immersion in sodium dichromate--sulfuric acid mixture.

Preparation of the Grignard reagent.--The usual procedure for the preparation of the Grignard reagent was as follows:

Fifty cc. of ether were poured into the flask, in which had been placed 5.2 g. of commercial magnesium turnings (less than 10% excess). One-fifth of a mole of the halide was dissolved in 50 cc. of ether, and a few cubic centimeters of this solution were introduced from a dropping funnel. The solution was gently warmed with a micro burner to start the reaction. Then stirring was begun and the remainder of the halide solution added at such a rate that the ether was gently refluxed without further external application of heat. After the addition of the halide was completed, stirring was continued until the mixture had cooled. The stirrer and mercury seal were then quickly removed and replaced by the siphon. The solution was filtered with slight suction (from a water pump) into a cooled graduated cylinder, which could be fitted with a glass stopper. Usually about 50 cc. of solution were collected. Two 2 cc. aliquots were removed for titration by the acid method.¹⁸

Addition of the Grignard reagent to the carbonyl compounds.--A solution of the two carbonyl compounds in ether was prepared, such that the mole ratio of the Grignard reagent to each of these was 10:7:7. The solution of the Grignard reagent was introduced dropwise into the solution of the carbonyl compounds, during which time the reaction flask was continuously swirled and cooled by repeated immersion in ice-water. The time

of completion of the addition was noted.

The mixture was allowed to stand at room temperature for a period of thirty minutes or four hours, at the end of which time it was hydrolyzed. Extraction with ether and drying of the ether extract with sodium sulfate followed. From this point slight variations depending on the particular compounds under investigation were necessary, and these will be described separately.

Analysis of Products

Determination of secondary alcohol in the presence of tertiary alcohol.--The analysis of the products was greatly simplified by choosing in all cases as the competing carbonyl compounds an aldehyde and a ketone. This permitted the direct determination of the secondary alcohol by the acetylation method of Freed and Wynne,²³ and the yield of tertiary alcohol was determined by difference (after accounting for unchanged reactants present in the mixture). In every case the applicability of the method was first tested on known samples of the pure alcohols (both secondary and tertiary), on known mixtures of both, and on mixtures of these with the aldehyde and ketone (in the experiments in which these unchanged reactants were not previously removed). The pure alcohols were prepared by the same reaction to be applied in the competitive experiments, and were carefully purified by distillation and crystallization (in the case of the solid products) prior to use. Crystallization was in all cases from ligroin, as any solvent which might interfere with the acetylation must be avoided. In general, it was found that this method of analysis yielded results within 5% of the calculated values, and in many cases an accuracy of about 2% was readily attained.

The general procedure for the acetylation of the alcohols was the same throughout. The acetylating agent consisted of a 12% solution of carefully dried acetic anhydride in anhydrous pyridine. This reagent darkens on standing, but may be kept in a glass-stoppered bottle for months without decreasing in efficiency. With each determination a blank was run on a sample of the reagent alone, and any change in the latter was thus taken into account. Actually it was found that the blank remained constant (within 0.10 cc. of 0.1 N sodium hydroxide) for several weeks.

²³Freed and Wynne, Ind. Eng. Chem., Anal. Ed., 8, 278 (1936).

A weighed, or pipetted, sample for analysis and a glass bead were introduced into an 18 mm. pyrex test tube. If the sample were a solution in ether, the solvent was then removed by careful warming on a steam bath. After the tube had cooled, 2 cc. of the reagent were introduced from a pipette²⁴ and an all-glass "cold finger" condenser²⁵ was placed in the test tube. The mixture was gently refluxed for one hour over the small flame of a micro burner. The contents of the tube were allowed to cool, then 5 cc. of carbon dioxide-free water were added. The mixture was poured into a 125 cc. Erlenmeyer flask, and both the tube and the outer walls of the condenser were successively washed with two 10 cc. portions of carbon dioxide-free water and one 10 cc. portion of 95% ethanol. The washings were combined with the hydrolyzed mixture, and the whole was titrated with carbon dioxide-free 0.1 N sodium hydroxide to the phenolphthalein end-point. In every determination involving the actual products of a competitive reaction, a correction to be applied for the acidity of the sample was separately determined. This correction was usually small, seldom above 0.15 cc. of 0.1 N sodium hydroxide, an amount well within the limits of the experimental error. The amount of secondary alcohol in the sample was calculated from the difference in titre for the blank and for the sample.²³

Sample determinations on known compounds are listed in Table IV.

Determination of benzaldehyde.--The method used was a direct application of that of Ferrante and Bloom.²⁶ The reagent was prepared by dissolving 2 g. of 2,4-dinitrophenylhydrazine in 5 cc. of concentrated sulfuric acid. Solution is readily achieved by stirring and warming on a steam bath. After cooling, the mixture was diluted with methanol to 50 cc. This solution deteriorates on standing for several days, and so it was freshly prepared prior to use.

The sample was dissolved in 25 cc. of methanol and to this was added with constant stirring 10 cc. of the reagent (ca., 10% excess). The mixture was allowed to stand overnight. The pre-

²⁴To avoid any error from this source the same pipette should be used throughout.

²⁵Olson and Plass, Ind. Eng. Chem., Anal. Ed., 7, 444 (1935).

²⁶Ferrante and Bloom, Am. J. Pharm., 105, 381-4 (1933).

TABLE IV
DETERMINATION OF ALCOHOLS BY ACETYLATION

Sample	M. Equivs. OH Calculated		M. Equivs. OH Found	% Error
	Secondary	Tertiary		
Benzhydrol	0.486	0.697	0.457	- 6.0
Phenyl cyclo- hexanol		1.39	0.01	+ 0.7
Benzhydrol	0.761	0.242	0.800	+ 5.1
Phenyl cyclo- hexanol		1.39	0.01	+ 0.7
Benzaldehyde	0.761	0.242	0.800	+ 5.1
Cyclohexanone		1.39	0.01	+ 0.7
Benzhydrol	1.15		1.125	- 2.2
Benzhydrol	1.30	1.36	1.28	- 1.5
Phenyldimethyl carbinol		2.00	0.168	+ 8.4
Phenyldimethyl carbinol	1.25	0.800	1.16	- 7.2
Benzhydrol	1.25	0.800	1.16	- 7.2
Phenylmethyltert.- butyl carbinol		1.11	0.002	+ 0.2
Phenylmethyltert.- butyl carbinol		1.11	0.002	+ 0.2
Phenylmethyl car- binol	1.68		1.58	- 6.0
Phenylmethyl car- binol	1.62	2.40	1.59	- 1.9
Phenyldimethyl carbinol	1.62	2.40	1.59	- 1.9
Phenylbenzyl car- binol	1.39		1.31	- 5.8 ^a
Phenylbenzyl car- binol	2.03	3.49	1.76	-13.3 ^a
Benzyl cyclohexanol	2.03	3.49	1.76	-13.3 ^a
Benzyl cyclohexanol		2.19	0.04	+ 1.8

^aRelatively large error probably due to incomplete removal of solvent (ligroin) from the recrystallized alcohol.

precipitated 2,4-dinitrophenylhydrazone of benzaldehyde was separated by filtration through a weighed sintered glass (100 mesh) funnel. The precipitate was washed with 15 cc. of acidified methanol (100 cc. of methanol plus 1 cc. of concentrated sulfuric acid),

then with 10 cc. of methanol. The product was dried for two hours in an electric oven at 75°C.

The results of two determinations are given in Table V:

TABLE V
GRAVIMETRIC DETERMINATION OF BENZALDEHYDE

No.	Sample	Weight	Weight of Product	M. P. ^a of Product	% Benzaldehyde Found
1	Benzaldehyde Benzhydrol	0.196 g. 0.20 g.	0.525 g.	235-7°	99.5
2	Benzaldehyde Benzhydrol Phenyldimethyl carbinol	0.196 g. 0.10 g. 0.30 g.	0.510 g.	234-6°	96.5

^aReported melting-point, 235°. ²⁷

Determination of pinacolone.--The reagent used was the same as for the determination of benzaldehyde, but slight modifications in the procedure were necessary because of the greater solubility of the 2,4-dinitrophenylhydrazone of pinacolone. The following procedure was adopted:

The sample was dissolved in 10 cc. of methanol and treated with 10 cc. of the reagent (ca., 25% excess). The flask was well shaken, but no precipitate appeared until a few minutes after the addition of the reagent. Five hours after mixing, 10 cc. of 6 N sulfuric acid were added and the flask was vigorously swirled. The mixture was allowed to stand overnight. The precipitate was separated by filtration through a weighed sintered glass (100 mesh) funnel, washed with 10 cc. of 2 N sulfuric acid (one volume of 6 N sulfuric acid plus two volumes of methanol), and finally with 10 cc. of 20% methanol. The product was dried for two hours in an electric oven at 75°C.

The results of two determinations are given in Table VI.

Preparation of the Condensation Products

It has already been mentioned that each of the products expected in the competitive reactions was prepared in pure form by the identical reaction to be used in the competitive experi-

²⁷Curtius and Dedichen, J. prakt. Chem., **50**, 265 (1894).

TABLE VI
GRAVIMETRIC DETERMINATION OF PINACOLONE

No.	Sample	Weight	Weight of Product	M. P. ^a of Product	% Pinacolone Found
1	Pinacolone	0.149 g.	0.404 g.	123-5°	96.7
2	Pinacolone Benzhydrol	0.149 g. 0.20 g.	0.408 g.	123-5°	97.8

^aReported melting-point, 125°. ²⁸

ments proper. This was done to make the products available for the acetylation experiments. However, this requirement alone would not warrant restriction to this mode of preparation, especially since some of the products are more readily prepared and in greater yield by other methods; e.g., phenylmethyl carbinol by the reduction of acetophenone or from the action of methylmagnesium iodide on benzaldehyde, rather than from phenylmagnesium bromide and acetaldehyde. Since it was necessary to ascertain the identity of the products resulting from a definite procedure, the reason for the precaution is evident. A noteworthy example is the reaction of phenylmagnesium bromide with acetone. If the addition product is hydrolyzed with dilute hydrochloric acid and then extracted with ether, β -phenylpropylene (B. P., 60-3°/ 18 mm.) is obtained in 30% yield.²⁹ If, however, the hydrolysis is with dilute acetic acid and the excess acid is neutralized with sodium carbonate prior to removal of the ether, then the normal product phenyldimethyl carbinol (B. P., 93-7°/ 18 mm.) is obtained and not a trace of the olefine is detectable. In general it may be mentioned that the hydrolyzing agent plays an important part in the determination of the nature of the product, especially if no precautions are taken to remove any excess reagent (particularly in the case of acids) before proceeding further. These remarks apply to many secondary alcohols, which are readily dehydrated to the ethers, and to many tertiary alcohols, which are dehydrated to the corresponding olefines.

²⁸Allen, J. Am. Chem. Soc., 52, 2958 (1930).

²⁹Harries, Ann., 390, 265 (1912), has reported the formation of β -phenylpropylene from phenyldimethyl carbinol and hydrochloric acid.

The products prepared are listed in Table VII. No special precautions were taken to ensure high yields, as the purity of the product was of prime consideration.

TABLE VII
PREPARATION OF CONDENSATION PRODUCTS.

Product	Prepared from	B. P.	M. P.	Yield
Benzhydrol	Phenylmagnesium bromide and benzaldehyde	180°/ 20 mm.	68°	...
Phenyl cyclohexanol	Phenylmagnesium bromide and cyclohexanone	...	59-61°	48%
Phenyldimethyl carbinol	Phenylmagnesium bromide and acetone	93-7°/ 18 mm.	29-30° ^a	36%
Phenylmethyl-tert.-butyl carbinol	Phenylmagnesium bromide and pinacolone	111-4°/ 10 mm.	...	5%
Phenylmethyl carbinol	Phenylmagnesium bromide and acetaldehyde	95-8°/ 17 mm.	...	69%
Phenylbenzyl carbinol	Benzylmagnesium chloride and benzaldehyde	166-9°/ 10 mm.	66- 7°	26% ^b
Benzyl cyclohexanol	Benzylmagnesium chloride and cyclohexanone	155-8°/ 20 mm.	53- 5°	11% ^b

^aMelting-point reported by Grignard,³⁰ 23°; but Perkin and Matsubara³¹ reported 35-7°.

^bThe author is pleased to acknowledge his indebtedness to Mr. Elias Sternfeld of this laboratory for the preparation of these compounds.

Competitive Reactions

Addition of phenylmagnesium bromide to a mixture of benzaldehyde and cyclohexanone.--The addition product was hydrolyzed with an equivalent quantity of 1 N acetic acid. Extraction with ether isolated the products and unchanged reactants in the ether fraction. After removal of the ether, the mixture was steam distilled until the odors of benzaldehyde and cyclohexanone were no longer noticeable in the distillate. The cooled residue in the flask was extracted with ether, and the extract dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration through a plug of cotton, and the ether by distillation

³⁰Grignard, Ann. chim. phys. (7), 24, 471 (1901).

Tissier and Grignard, Compt. rend., 132, 683, 1184 (1901).

³¹Perkin and Matsubara, J. Chem. Soc., 87, 671 (1905).

from a steam bath. The residue (containing a small amount of unchanged aldehyde and ketone as well as the products of reaction) was weighed and 0.5 cc. aliquots taken as samples for acetylation. This determined the total yield of benzhydrol. The remaining residue was further distilled with steam, a white crystalline solid separating in the distillate. The solid was filtered, washed with water, and dried. It was then weighed and thoroughly pulverized in a mortar (to ensure homogeneity of sample). Weighed aliquots were taken for acetylation, and the percentage of benzhydrol in the solid was determined. On the assumption³² that this percentage corresponds to the total yield of benzhydrol relative to the combined yields of benzhydrol plus phenyl cyclohexanol, the total yield of phenyl cyclohexanol in the experiment was calculated.

The results of the experiments are listed in Table VIII.

It should be mentioned that in one experiment, in which the mole ratio of phenylmagnesium bromide to benzaldehyde and cyclohexanone was about 1:3:3, an unusual reaction occurred. Instead of the expected condensation of the carbonyl compounds with the Grignard reagent, the aldehyde and ketone condensed with each other forming 2,6-dibenzylidenecyclohexanone.³³ This condensation did not occur if the mole ratio was 1:1:1, or if the proportion of the Grignard reagent was even higher.

Addition of phenylmagnesium bromide to a mixture of benzaldehyde and acetone.--The addition product was hydrolyzed with an equivalent quantity of 1 N acetic acid. The mixture was treated with excess sodium carbonate to neutralize any excess acid. The mixture was then filtered with suction and the residue on the filter paper was washed several times with ether. The filtrate and washings were combined, extracted with ether, and the ether frac-

³²That this assumption was justified was shown by determining the volatilities of benzhydrol and phenyl cyclohexanol with steam. Sixty to seventy per cent recovery of pure product in the distillate was realized in each case. That the relative volatilities of the two compounds with steam are approximately equal was further shown by steam distilling a known mixture of the two and subsequently determining the percentage of benzhydrol in the solid distillate. This agreed within 5% of the calculated value for the original known mixture. The procedure is further justified by the fact that more than 95% of the reactants were accounted for in the competitive experiments analyzed by this method.

³³Wallach, Chem. Zentr., 1908 I, 638.

TABLE VIII
REACTION OF BENZALDEHYDE AND CYCLOHEXANONE WITH
PHENYLMAGNESIUM BROMIDE

Run No.	Normality of Grignard Solution	Yield ^a		Total Yield	Reactivity Ratio (A/K) ^c
		Secondary ^b	Tertiary ^b		
11	1.19 N	42.8%	8.3%	51.1%	5.16
12	2.09 N	41.7%	7.4%	49.1%	5.65
13 (*) ^d	0.694 N	32.6%	5.0%	37.6%	6.52

^aAll yields in this and subsequent tables are calculated on the basis of the Grignard reagent added.

^b"Secondary" and "tertiary" refer to the secondary alcohol and the tertiary alcohol formed by the reaction of the Grignard reagent with the aldehyde and ketone respectively.

^cThe ratio A/K denotes the relative reactivities of the aldehyde and ketone based on the ratio of the yields of their respective addition products in the competitive reaction. The ratio K/A is merely the reciprocal of A/K.

^dRuns denoted by (*) are half-hour runs; others are four-hour runs. The time refers to the interval between the completion of addition and the hydrolysis.

tion dried with anhydrous sodium sulfate. After removal of the drying agent and distillation of the ether, there were left in the flask the products of the reaction plus unreacted benzaldehyde. The total residue was weighed, and then washed with saturated sodium bisulfite solution. The washing was twice repeated, and the combined aqueous fraction and precipitate were washed with ether. The recovered benzaldehyde was then determined by treating the precipitate and aqueous fraction with excess 10% sodium carbonate solution, warming to 70-80°, extracting the cooled mixture with ether, drying the ether extract, and finally weighing the residue after removal of the drying agent and distillation of the ether.

The combined ether washings and ether fraction from the bisulfite treatment were dried with sodium sulfate. After removal of the sodium sulfate and distillation of the ether, the cooled residue was weighed. This was diluted with anhydrous ether to 50 cc., and 5 cc. aliquots of this solution were taken as samples to be acetylated. Another 5 cc. portion was taken for the determination of the acid content of the solution. Finally one 5 cc. portion was taken to determine the efficiency of the bisulfite

treatment for removal of the benzaldehyde. This was tested by distilling the ether, dissolving the residue in methanol, and treating the solution with 2,4-dinitrophenylhydrazine reagent. No precipitate was formed. The yield of benzhydrol was calculated from the acetylation determination, and the yield of phenyldimethyl carbinol was determined by difference. The results are in Table IX:

TABLE IX
REACTION OF BENZALDEHYDE AND ACETONE WITH
PHENYLMAGNESIUM BROMIDE

Run No.	Normality of Grignard Solution	Yield		Total Yield	Reactivity Ratio (K/A)
		Secondary	Tertiary		
16	1.69 N	21.6%	62.9%	84.5%	2.91
17	1.72 N	21.6%	61.2%	82.8%	2.83
18 (*)	1.90 N	16.2%	56.7%	72.9%	3.50

Addition of phenylmagnesium bromide to a mixture of benzaldehyde and pinacolone.--The addition product was hydrolyzed by pouring the mixture into ice-water. The mixture was allowed to stand overnight, and was then decanted and filtered with suction. The residue on the filter paper was washed several times with ether, and the combined filtrate and washings were extracted with ether. After drying the ether fraction, the drying agent was removed and the ether distilled. The cooled residue was weighed. This contained the products and unchanged reactants. The residue was diluted with dry ether to 50 cc.

Two cc. aliquots of this solution were taken for acetylation and for acidity determination. This gave the yield of benzhydrol. The benzaldehyde was determined by the bisulfite method.³⁴ The ether extract from the bisulfite treatment was dried. After removal of the drying agent and distillation of the ether, the residue was dissolved in methanol and diluted to 50 cc. Two cc. aliquots of this solution were diluted with methanol to

³⁴Cf., *supra*, p. 21. This precaution is necessary to ensure the precipitation of the 2,4-dinitrophenylhydrazone of pinacolone only in the following determination. A part of the pinacolone is undoubtedly removed by the bisulfite treatment. This is not objectionable, since it is the combined weight of the recovered aldehyde and ketone which is ultimately sought.

10 cc. and the pinacolone determined by the 2,4-dinitrophenylhydrazine method.³⁵ In calculating the total recovered benzaldehyde and pinacolone a correction was made for that portion lost in the samples taken for acetylation. The yield of phenylmethyl-tert.-butyl carbinol was calculated by difference.

The results of these experiments are listed in Table X:

TABLE X
REACTION OF BENZALDEHYDE AND PINACOLONE WITH
PHENYLMAGNESIUM BROMIDE

Run No.	Normality of Grignard Solution	Yield		Total Yield	Reactivity Ratio (A/K)
		Secondary	Tertiary		
21	1.83 N	32.7%	28.6%	61.3%	1.14
22	2.00 N	39.2%	44.2%	83.4%	0.89
23 (*)	1.65 N	47.3%	42.1%	89.4%	1.12

Addition of phenylmagnesium bromide to a mixture of acetaldehyde and acetone.--Special precautions were taken in the addition to avoid loss of the extremely volatile acetaldehyde. The addition was carried out in a 250 cc. Erlenmeyer flask immersed in ice. The flask was equipped with a trident adapter, the vertical arm of which was a mercury seal. The two side-arms accommodated a reflux condenser and a dropping funnel. The solution of the carbonyl compounds in ether was introduced into the flask through the dropping funnel, which was then washed with 10 cc. of ether (and the washings allowed to run into the flask). The solution of the Grignard reagent was added slowly and with constant stirring to the mixture in the flask. The time of completion of the addition was noted.

After standing the requisite period of time the mixture was hydrolyzed with ice-water. Filtration, extraction with ether, drying, and subsequent removal of the drying agent and ether followed in the manner previously described.³⁶ Because of the miscibility of acetaldehyde and acetone with water and because of their low boiling-points, these are completely removed by this treatment. The final residue contains only the products of the reaction, and is weighed as such. The residue was then diluted with

³⁵ Supra, p. 17.

³⁶ Supra. p. 22, paragraph 1.

dry ether to 50 cc., and 2 cc. aliquots were removed for acetylation and determination of acid content. From this the yield of phenylmethyl carbinol was calculated, and the yield of phenyldimethyl carbinol was determined by difference. The results are given in Table XI:

TABLE XI
REACTION OF ACETALDEHYDE AND ACETONE WITH
PHENYLMAGNESIUM BROMIDE

Run No.	Normality of Grignard Solution	Yield		Total Yield	Reactivity Ratio (K/A)
		Secondary	Tertiary		
25	1.70 N	29.3%	42.3%	71.6%	1.45
26	1.53 N	33.6%	48.0%	81.6%	1.43
27 (*)	1.63 N	30.0%	46.0%	76.0%	1.53

Addition of benzylmagnesium chloride to a mixture of benzaldehyde and cyclohexanone.--The addition product was hydrolyzed with ice-water, and the mixture treated in the usual manner.³⁶ The residue from the ether distillation was weighed and then diluted with dry ether to 50 cc. This contains the products plus unchanged reactants. Two cc. aliquots of this solution were taken for acetylation and determination of acidity, from which the yield of phenylbenzyl carbinol was calculated. The remainder of the ether solution was then treated with sodium bisulfite in the manner previously described.³⁴ Both the benzaldehyde and cyclohexanone are efficiently removed by this method, as may be shown by the application of the 2,4-dinitrophenylhydrazine test³⁷ to a portion of the ether fraction remaining from the bisulfite treatment. The combined weight of recovered benzaldehyde and cyclohexanone is thus determined, and the correction is applied for the fraction used in the acetylation and acidity determinations. The yield of benzyl cyclohexanol was calculated by difference. The results are in Table XII.

Addition of phenylmagnesium bromide in pyridine to a mixture of benzaldehyde and acetone in pyridine.--The pyridine was carefully purified and dried by refluxing for three hours over barium oxide and then distilling the decanted liquid through a

³⁷ Supra, pp. 21 f.

Schneider fractionating column. The pyridine was stored over barium oxide in a dark stock bottle from which air and moisture were carefully excluded.

TABLE XII
REACTION OF BENZALDEHYDE AND CYCLOHEXANONE WITH
BENZYL MAGNESIUM CHLORIDE

Run No.	Normality of Grignard Solution	Yield		Total Yield	Reactivity Ratio (A/K)
		Secondary	Tertiary		
32	1.61 N	47.0%	33.1%	80.1%	1.45
33	0.909 N	56.7%	41.3%	98.0%	1.37

The method of preparing the Grignard reagent solution in pyridine, which has been described by Kharasch and Weinhouse,³⁸ was not satisfactory for this purpose. On the addition of the pyridine to the "anhydrous" Grignard reagent, a vigorous exothermic reaction occurred. By very careful addition the loss of reagent through spattering could be minimized, but the mixture solidified on cooling and it was impossible to obtain a satisfactory homogeneous solution. The following procedure was adopted:

The solution of the Grignard reagent in ether was added slowly from a dropping funnel to 50 cc. of anhydrous pyridine. The mixture was mechanically stirred and the reaction flask cooled in ice during this operation. The trident adapter already mentioned³⁹ was used. After completion of the addition, the adapter was removed and replaced by a large Kjeldahl trap which was attached to the water pump. Suction was carefully applied to remove the ether. After thirty minutes of this treatment, the flask was surrounded with warm water (60°) for ten minutes to facilitate the removal of the remaining ether. After the contents of the flask had cooled, an additional 100 cc. portion of pyridine was added. All of the pyridine-phenylmagnesium bromide complex did not go into solution, but remained as a finely divided yellow-gray suspension in a green-brown solution.

This solution and suspension were slowly added to the solution of the carbonyl compounds in pyridine, the reaction flask

³⁸Kharasch and Weinhouse, op. cit., p. 226.

³⁹Supra, p. 23.

being well shaken and cooled during the addition. It was noted that heat was evolved and the color of the supernatant liquid changed to deep orange.

The mixture was hydrolyzed with ice-water and filtered. The residue on the filter paper was washed with several portions of ether, and the washings were added to the filtrate. The latter was then saturated with sodium chloride and extracted with ether. After removal of the ether from the ether extract, the liquid remaining was treated with an excess of dilute acetic acid. The mixture was extracted with ether, and the ether extract was washed with three successive portions of dilute acetic acid, and finally with 10% sodium carbonate solution in two 50 cc. portions. The ether fraction was dried with sodium sulfate, and then the drying agent was removed and the ether distilled. The residue was dried in a vacuum desiccator over phosphorus pentoxide for four hours. If the odor of pyridine was still detectable after this treatment, the acid washing and subsequent treatment were repeated until the odor of pyridine was absent from the product. This was weighed and diluted with dry ether to 50 cc.

Two cc. aliquots of this solution were taken for determination of acidity, of benzhydrol by the acetylation method, and of benzaldehyde by the 2,4-dinitrophenylhydrazine method.⁴⁰ The yield of phenyldimethyl carbinol was determined by difference.

The results are listed in Table XIII:

TABLE XIII
REACTION OF BENZALDEHYDE AND ACETONE IN PYRIDINE WITH
PHENYLMAGNESIUM BROMIDE IN PYRIDINE

Run No.	Yield		Total Yield	Reactivity Ratio	
	Secondary	Tertiary		(A/K)	(K/A)
30	30.0%	23.3%	53.2%	1.29	0.77
31	34.9%	25.0%	59.9%	1.39	0.72

Sensitivity of the Color Test¹⁹ for
Reactive Grignard Reagent

To each of a series of test tubes were added 0.5 cc. of a 1% solution of Michler's ketone in dry benzene plus a definite amount of a 1% solution of pure benzaldehyde in dry benzene:

⁴⁰Supra, pp. 15 ff.

<u>g. Michler's ketone</u>	<u>Test</u>
g. benzaldehyde	
∞	+
50:1	+
25:1	+
10:1	+
5:1	+
5:2	+
5:3	+
1:1	+
1:2	+
1:3	+
1:4	-
1:5	-
1:10	-
1:20	-
1:50	-

⁴¹Gilman and co-workers have used the color test to determine the time of completion of reaction of organometallic compounds with benzonitrile, benzaldehyde and benzophenone.

Gilman and Young, J. Org. Chem., 1, 315-31 (1936).

determined by checking with another method; e.g., the treatment with an ether solution of mercuric chloride. As has been demonstrated,⁴² the latter test may be positive when the color test is negative. If the substance competing with Michler's ketone is one which reacts with the Grignard reagent at the same or a slower rate, then the color test may be valid for the particular case.

⁴²Supra, p. 9.

SUMMARY

1. The literature on the relative reactivities of carbonyl compounds has been reviewed and the applicability of the data discussed.

2. The relative reactivities of a series of aldehydes and ketones toward the Grignard reagent have been studied. It is concluded that specific effects of solvents on condensation reactions of carbonyl compounds make impossible general statements about the relative reactivities of aldehydes and ketones.

3. The acetylation method for the determination of secondary alcohols in the presence of tertiary has been extended.

4. Satisfactory methods for the gravimetric determination of benzaldehyde and pinacolone as the 2,4-dinitrophenylhydrazones have been developed.

5. The limitations of the Gilman color test for reactive Grignard reagent are discussed.

